第30章
ANTIDEPRESSANT AGENTS

※ *GENERAL CONCEPTS*

A.憂鬱症之定義:

憂傷的期限與強度足以使一個人之生活能力喪失。

B.**憂鬱症之症狀 (Depressive Syndromes) :**

是一種情感的疲患，以情緒之改變為特徵:

depression (憂鬱- major), dysthymia (心情惡劣 - minor).

包括: 感情淡漠 (apathy)、無助感 (hopelessness)、罪惡感 (guilt)、對工作或家庭失去興趣、內心充滿悲觀與死亡之念頭。

※ *GENERAL CONCEPTS*

C. **憂鬱症之分類:**

1. Reactive or Secondary Deprssion

→大部分為此類型，佔 60%以上。

→因受到災難、挫折、疾病、藥物作用與精神障礙...等所致

2. Endogenous Depression

→ > 25%

→ biochemical disorder 所致，無力承受一般之 stress。

3. Bipolar Affective Disorder (Manic-depressive Disorder)

→10-15 %

→乃躁症與鬱症交替發作。

* 神經營養假說 Neurotrophic Hypothesis

·由研究顯示，神經生長因子 (nerve growth factors)

如 brain-derived neurotrophic factor (BDNF)

對於神經可塑性 (plasticity),彈性 (nesilience) 及

神經再生 (neurogenesis) 具有調節作用。

∴ depression 與神經營養失調有關

·antidepressant 治療後，在 hippocanpus 出現增強神經

之再生及連結。

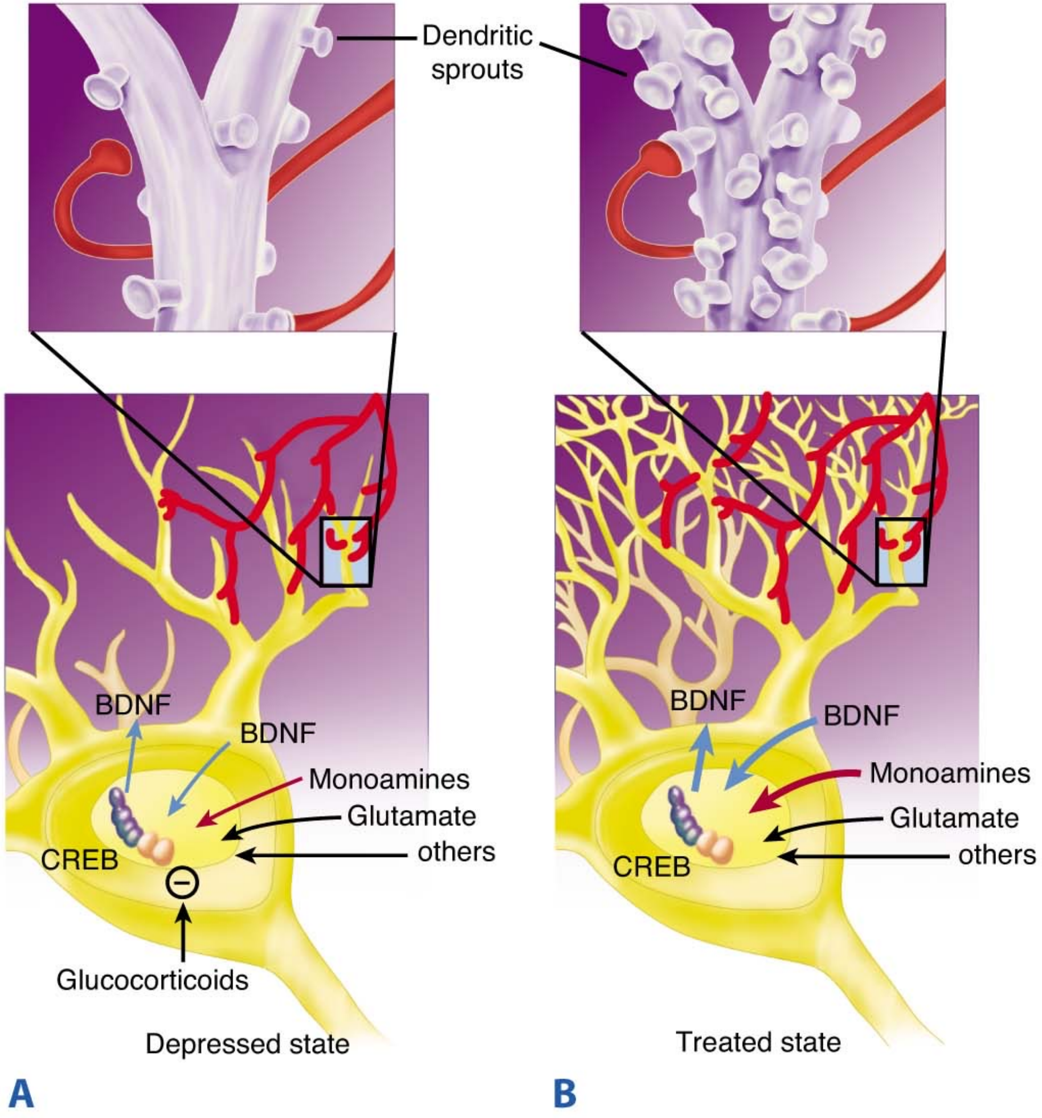


FIGURE 30–1 The neurotrophic hypothesis of major depression. Changes in trophic factors (especially brain-derived neurotrophic factor, BDNF) and hormones appear to play a major role in the development of major depression (**A**). Successful treatment results in changes in these factors (**B**). CREB, cAMP response element-binding (protein). BDNF, brain-derived neurotrophic factor. (Redrawn, with permission, from Nestler EJ: Neurobiology of depression. Neuron 2002;34[1]:13–25.)

THE PATHOGENESIS OF MAJOR DPRESSION: THE AMINE HYPOTHESIS

- Reserpine
  - 1950年，Reserpine 在治療高血壓與精神分裂症時，發現其會誘發憂鬱 (depression) 之現象。
  - Mechanism of Reserpine：抑制 amine neurotransmitters (NE,5-HT) 在突觸前神經末端 vesicles之貯存。
  - 由於 reserpine 會induced-depression，且可 depleted stores of amine transmitters

➡故推測 Depression 可能與降低 amine-dependent transmitters 功能有關。

註：5-HIAA尿中濃度增加，診斷腫瘤

※ THE PATHOGENESIS OF MAJOR DPRESSION : THE AMINE HYPOTHESIS

- **Tricyclic & MAO Inhibitor**
  - Antidepressants
  - Mechanism of Tricyclic & MAO Inhibitor
    - blockade of reuptake or MAO inhibition.
- **Bupropion (第二代)**
  - Antidepressants。
  - Mechanism of Bupropion:
    - 與 NE, 5-HT之 storage,metabolism or reuptake 有關.

    ➡故 Depression 可能與 amine transmitters 之生化異常有關。

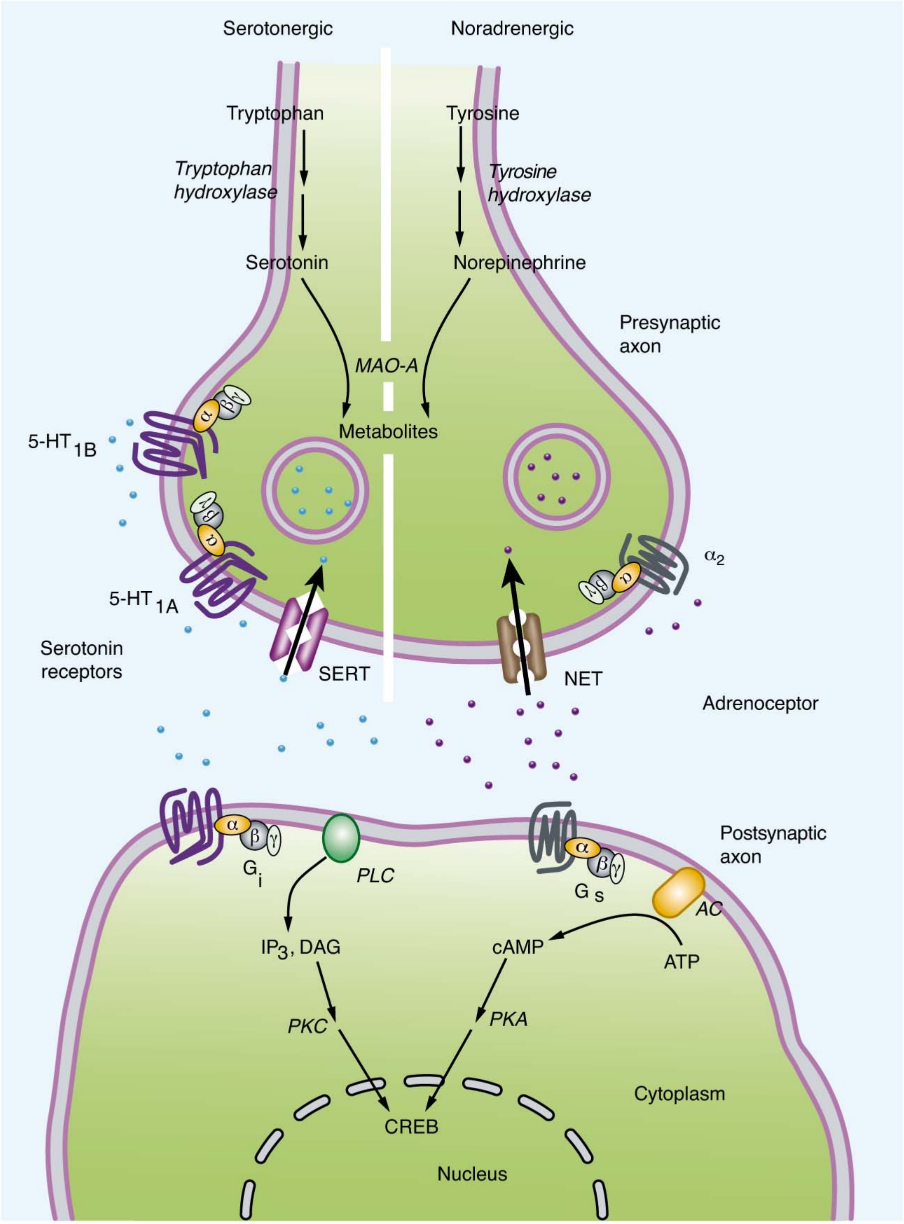


FIGURE 30–2 The amine hypothesis of major depression. Depression appears to be associated with changes in serotonin or norepinephrine signaling in the brain (or both) with significant downstream effects. Most antidepressants cause changes in amine signaling. AC, adenylyl cyclase; 5-HT, serotonin; CREB, cAMP response element-binding (protein); DAG, diacyl glycerol; IP_3, inositol trisphosphate; MAO, monoamine oxidase; NET, norepinephrine transporter; PKC, protein kinase C; PLC, phospholipase C; SERT, serotonin transporter. (Redrawn, with permission, from Belmaker R, Agam G: Major depressive disorder. N Engl J Med 2008;358:59.)

* Basic Pharmacology of Antidepressants

A. Selective serotonin Reuptake inhibitors (SSRIS):

本類藥物 primary action 在抑制 serotonin transporter (SERT)

- **Fluoxetine (Prozac)**

→自1988年起普遍使用於臨床。

→為 serotonin-reuptake inhibitor，具高選擇性

→對 histamine, acetylcholine, α adrenoceptor 之親和力低

→對 autonomic toxicity 低

- **Fluoxetine (Prozac)**
  - 臨床上用於:
    - GAD (generalized anxiety disorder)
    - PTSD (post-traumatic stress disorder 外傷後壓力)
    - OCD (obsessive-compulsive disorder)
    - panic disorder
    - PMDD (premenstrual dysphoric disorder 經前不安)
    - Bulimia (貪食)

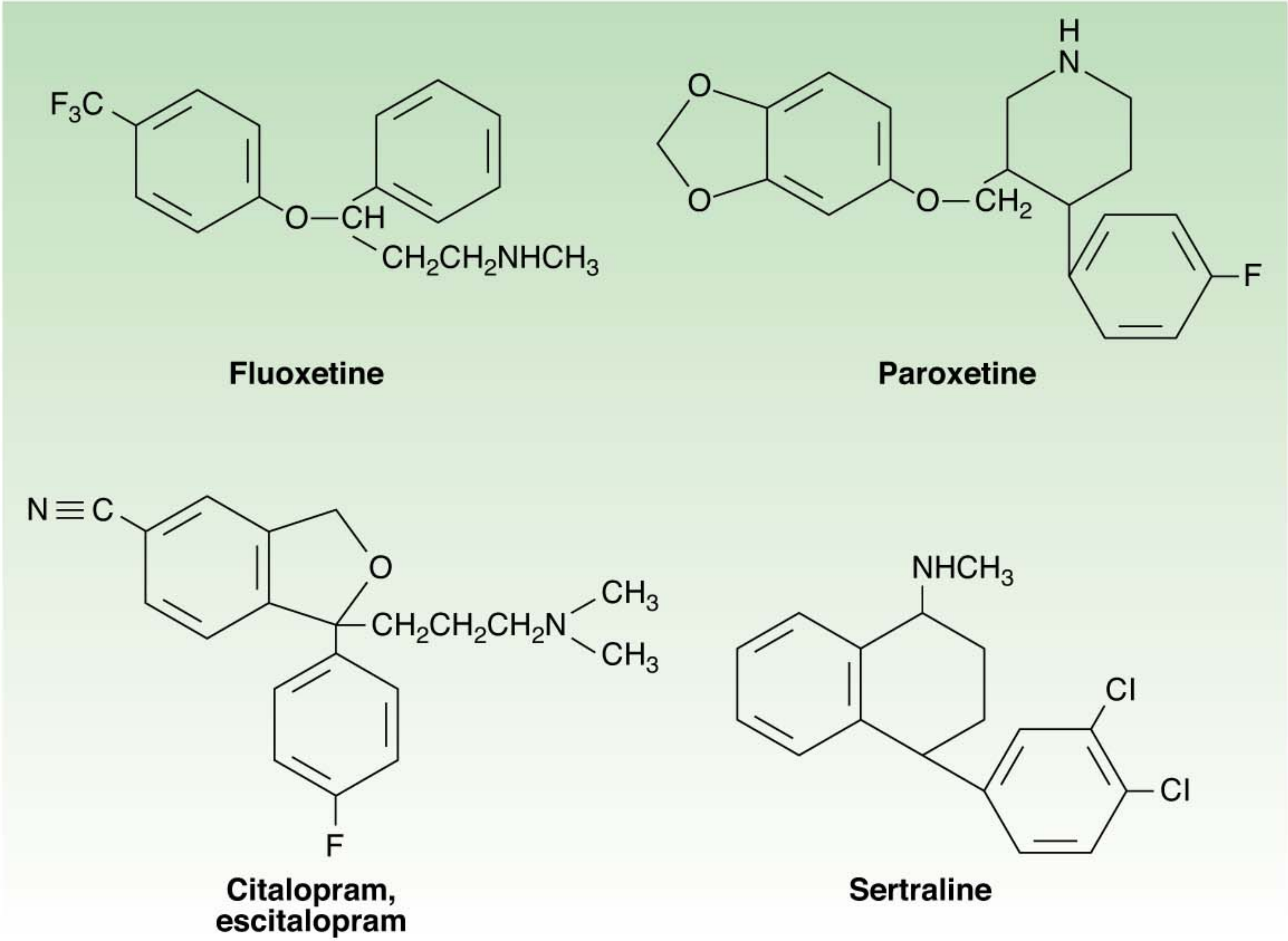


FIGURE 30–3 Structures of several selective serotonin reuptake inhibitors.

* Basic Pharmacology of Antidepressants

A. Selective serotonin Reuptake inhibitors ($SSRI_S$):

- Citalopram (Celexa)
- Escitalopram (Lexapro)
- Fluoxetine (Prozac)
- Fluvoxamine (只能用於obsessive-compulsive disorder)
- Paroxetine (Paxil)
- Sertraline (Zoloft)

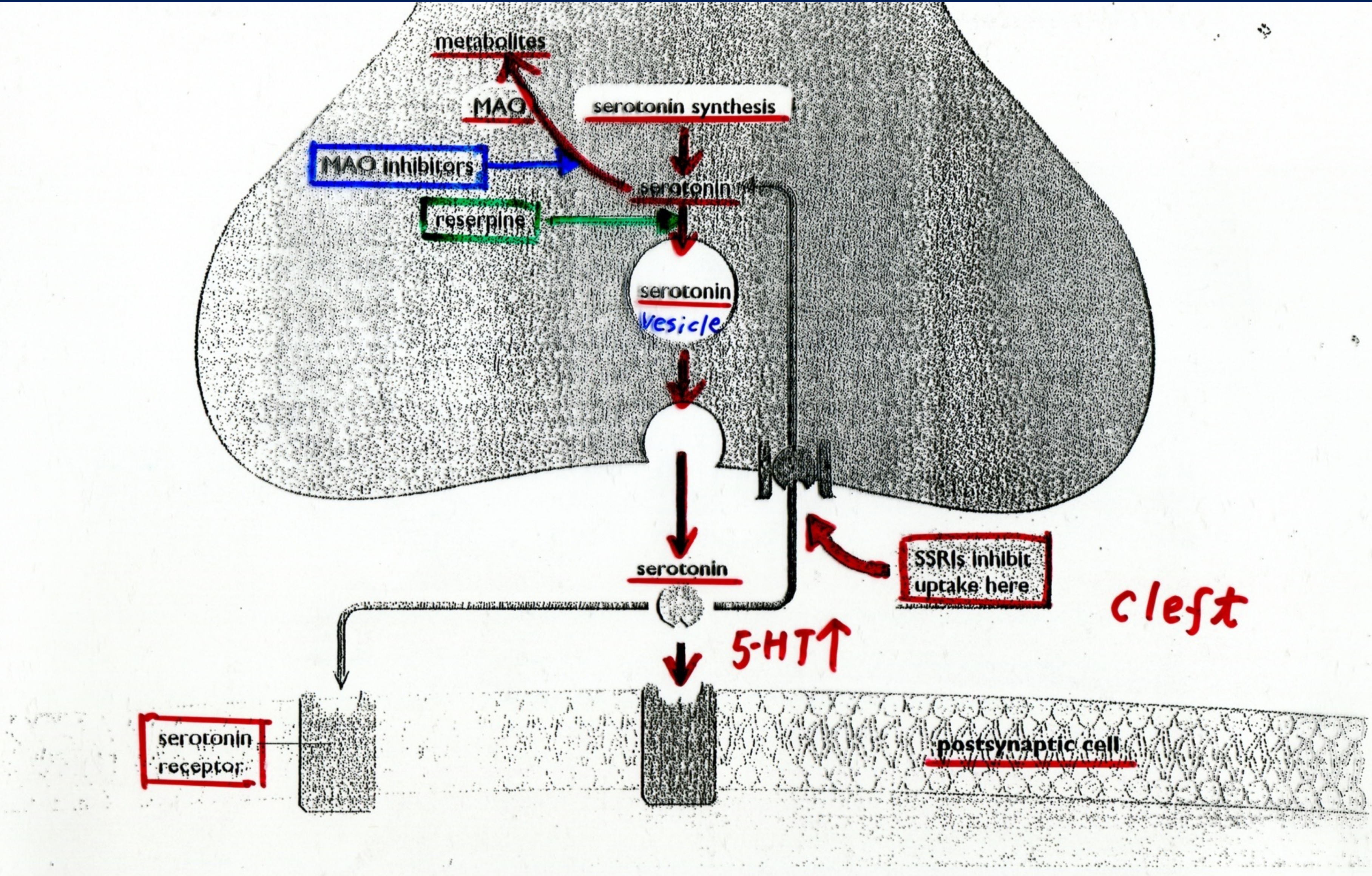


Fig. 14.42 Site of action of specific serotonin reuptake inhibitors (SSRIs) and monoamine oxidase (MAO) inhibitors. Reserpine leads to depletion of serotonin.

B. Serotonin-Norepinephrine Reuptake Inhibitors ($SNRI_S$)

1. Selective serotonin-norepinephrine reuptake inhibitors

·$SNRI_S$有Venlafaxine(Effexor),其代謝物 desvenlafaxine (Pristique).duloxetine (Cymbalta)

·構造式 p.514

·治療 pain disorders 包括神經質及 fibromyalgia (纖維肌痛: 全身酸痛，僵硬，疲勞)

·亦用於一般 anxiety，壓力性尿失禁 (stress urinary incontinence) 及更年期血管舒縮症狀 (vasomotor symptoms of menopause : 潮紅、夜間盜汗、心悸)

C. Tricyclic antidepressants (TCA_S)

·又稱 Thymoleptics (感情調整劑)

·於 1889 年合成 protriptyline, 1948 年發現有藥理作用，於1958年由 Kuhn 研究，但對 psychotic 病人無效，可是對 depression 病人有效。

·Amitriptyline (Elavil)

Amoxapine

Clomipramine (Anafranil, 僅使用於強迫行為)

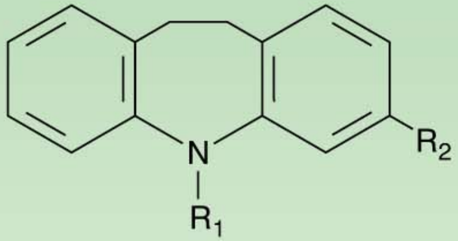
Desipramine (Norpramin)

Doxepin (Sinequan)

Imipramine (Tofranil)

Protriptyline (vivactil)

Trimipramine (Surmontil)



R_1:–$(CH_2)_3N(CH_3)_2$
R_2: H

Imipramine

R_1: = $(CH_2)_3NHCH_3$
R_2: H

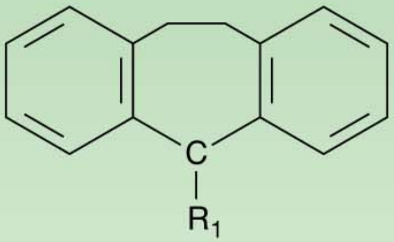
Desipramine

R_1: = $(CH_2)_3N(CH_3)_2$
R_2: – Cl

Clomipramine

R_1: = $CH_2CH(CH)_3CH_2N(CH_3)_2$
R_2: – H

Trimipramine

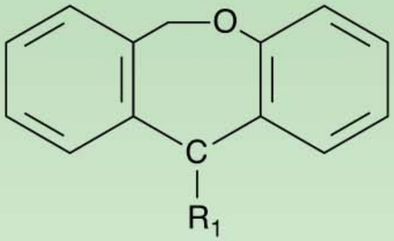


R_1: = $CH(CH_2)_2N(CH_3)_2$

Amitriptyline

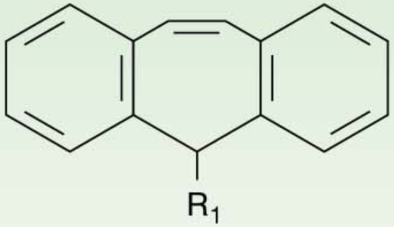
R_1: = $CH(CH_2)_2NHCH_3$

Nortriptyline



R_1: = $CH(CH_2)_2N(CH_3)_2$

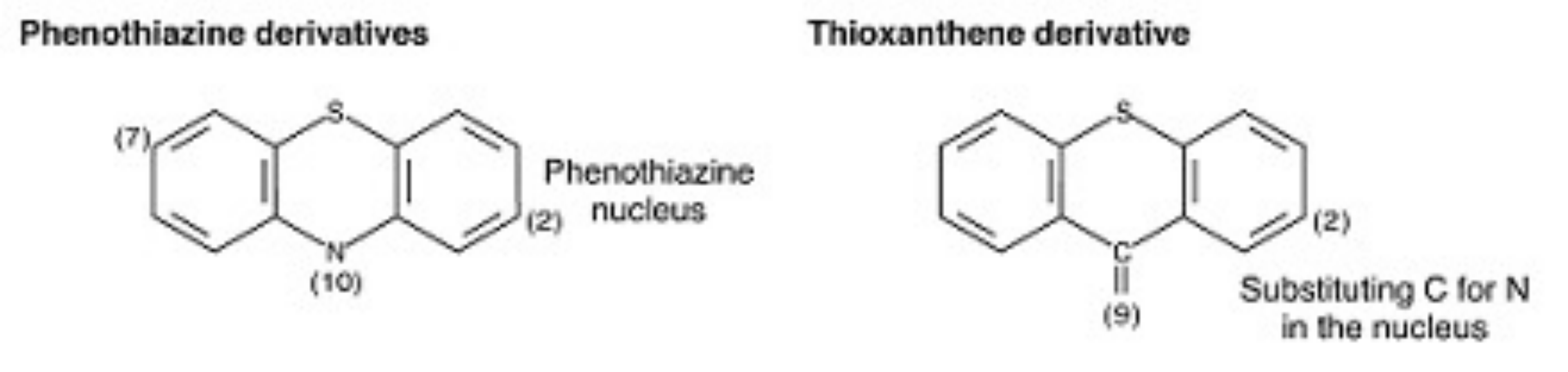
Doxepin



R_1: = $(CH_2)_3NCH_3$

Protriptyline

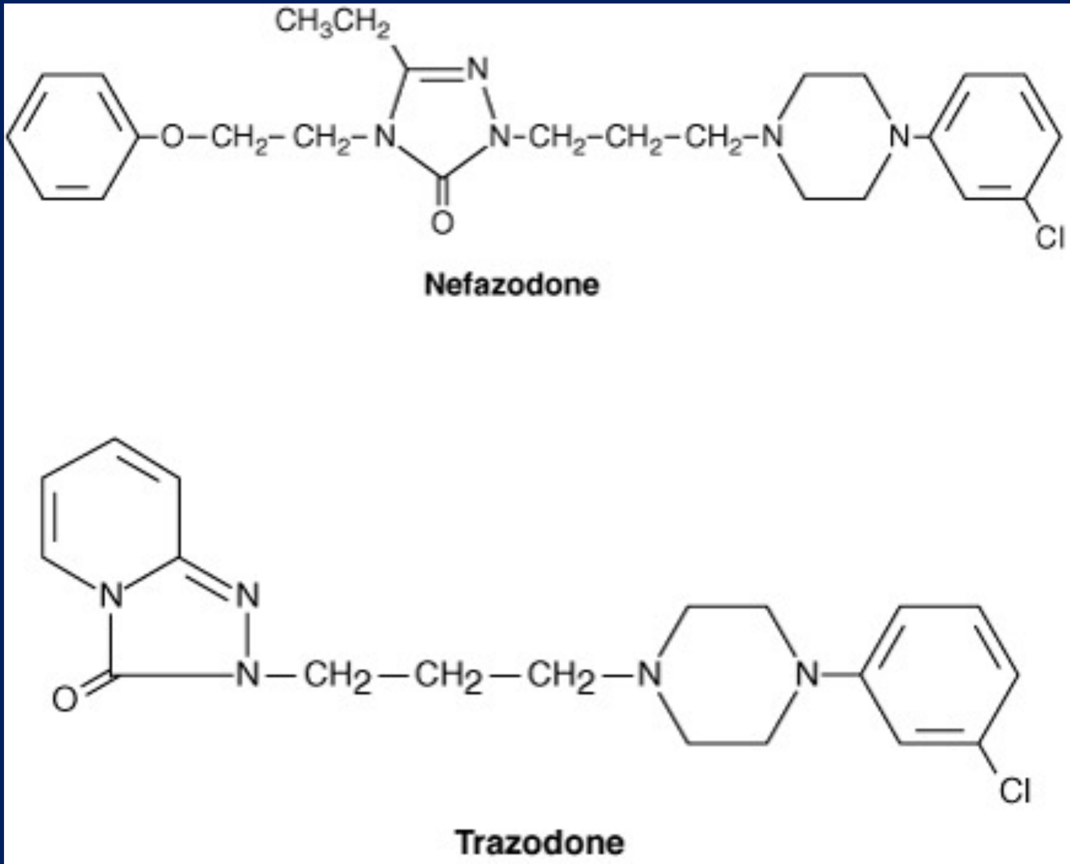
FIGURE 30–4 Structures of the tricyclic antidepressants (TCAs).



- 三環抗憂鬱劑之構造式與抗精神病之 phenothiazine 不同。即以 ethylene 取代 phenothiczine 之 sulfur
- 臨床上最常使用抗憂鬱劑，亦可用於疼痛、多尿，及不眠。

D. 5-HT$_2$ Antagonist

- Nefazodone : 於 2000 年 FDA 公告 hepatoxicity，致死性肝衰竭 (現今少用)。
- Trazodone: 用於 major depression, 也可用於 anxiety



E. Tetracyclic and unicyclic Antidepnessants

·Bupropion (wellbutrin) 構造式和 amphetamine 相似，

故有stimulant 及CNS ↑

·Amoxapine 是抗精神藥 loxapine 之代謝物，具有 DA antagonist.

·本品於 Major depressive disorder (MDD) 使用其他藥物無效時，選用之.

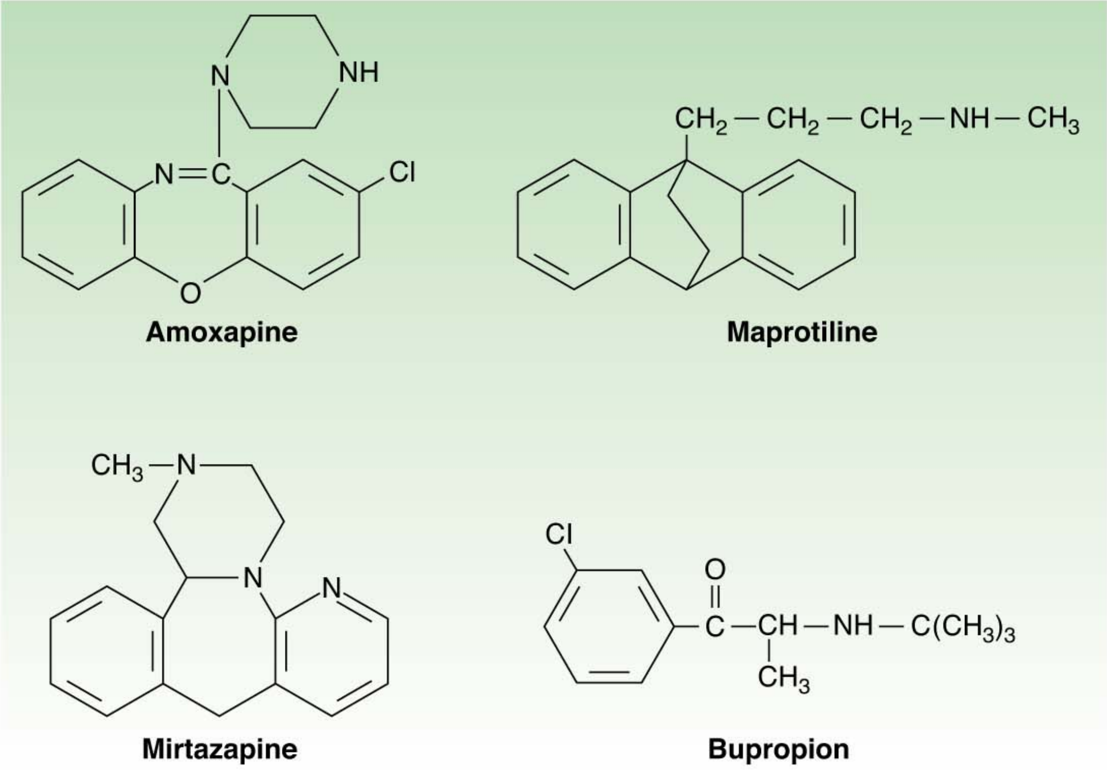
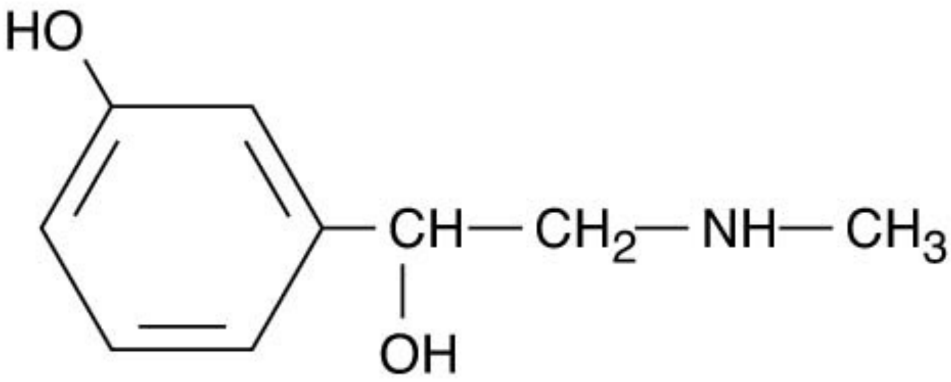
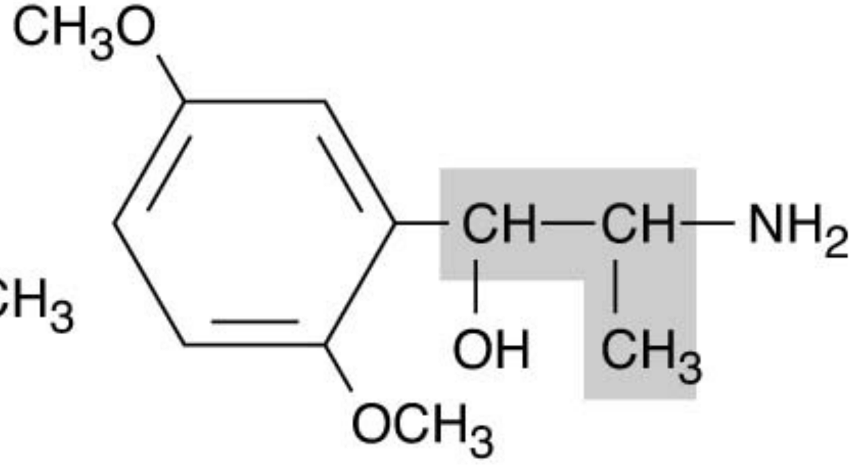


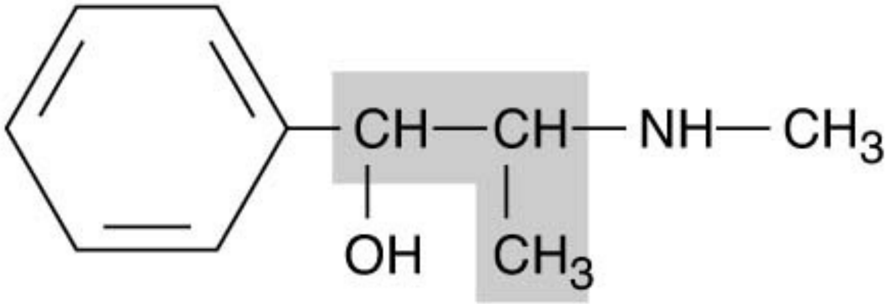
FIGURE 30–5 Structures of the tetracyclics, amoxapine, maprotiline, and mirtazapine and the unicyclic, bupropion.



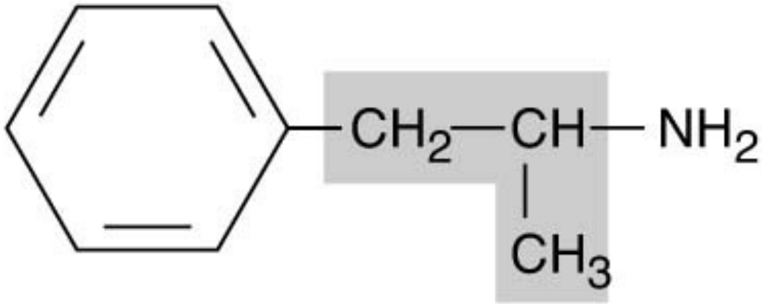
Phenylephrine



Methoxamine



Ephedrine



Amphetamine

FIGURE 9–5 Some examples of noncatecholamine sympathomimetic drugs. The isopropyl group is shown in gray.

F. Monoamine Oxidase Inhibitors ($MAOI_S$)

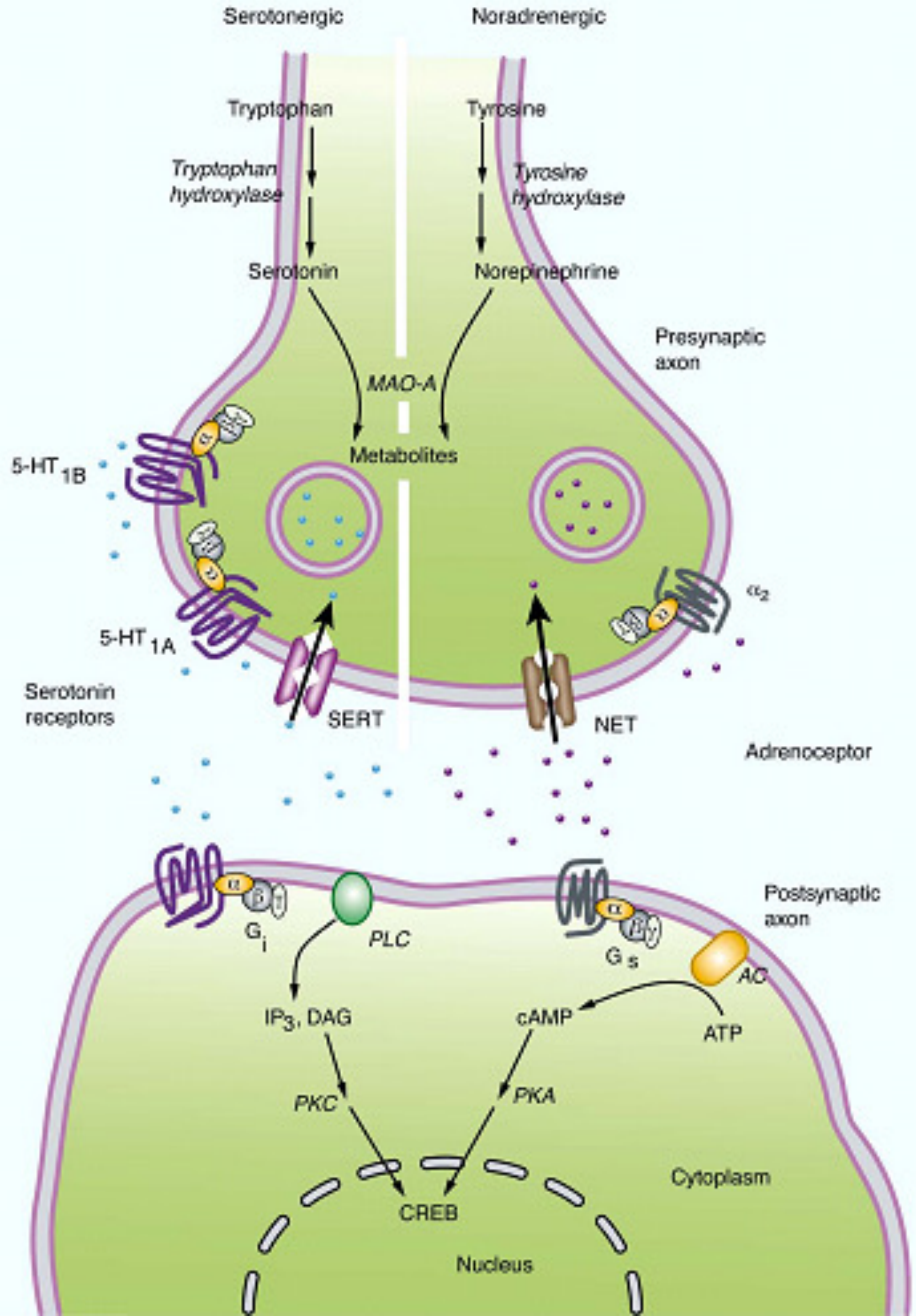
§·Hydrazide

→ phenelzine

·Non-nydrazide

→ tranylcypromine (Parnate)

·moclobemide (美國少用)



Monoamine oxidase
(MAO)

MAO_A 主要代謝 EPi, NE，5-HT

MAO_B 主要代謝 dopamin、tyramine

MAO_AI: Moclobemide

MAO_BI: Selegiline

MAO_AI+ MAO_BI
Phenelzine
Tranylcypromine
Isocarboxazide

* Pharmacokinetics

- **A. SSRI$_S$**

  Fluoxetine (半衰期 48-72 hr)

  →Active metabolite: norfluoxetine (活性) (半衰期7-9天)

  →此代謝物在血中濃度比原藥高，且半衰期長3倍。

  ∴不能使用超過4星期。

- Fluoxetine, paroxetine 是 CYP2D6 isoenzyme 之強力抑制劑

  →tamoxifen治療breast cancer必須受CYP2D6轉換成活性物，但Fluoxetine是CYP2D6之強力抑制劑，∴兩者不可併用

- Fluvoxamine 是 CYP3A4 抑制劑

  ∴本類藥品會抑制代謝藥物之 enzyme,

  故與其他藥品或 antipsychotics 併用應小心。

* Pharmacokinetics

B. $SNRI_S$

1. $SNRI_S$

– venlafaxine 在肝臟經由 CYP2D6 代謝成 O-esmethylvenlafaxine.

2.TCA_S

– 吸收不完全，分佈體積大

– Active metabolite

amitriptyline → nortriptyline

imipramine → desipramine

C. 5-HT_2 Antagonists

– Trazodone 由肝臟快速吸收、代謝。

D. Tetracyclic and Unicyclic Agents.

·Bupropion 約 85% protein binding.

→快速吸收

→經由肝代謝→ active metabolite (hydroxybupropion)

可成為 antidepressant.

→本品是 biphasic elimination

·first phase (1hr)

·second phase (14hr)

E. $MAOI_S$

·well absorbed (from GI)

TABLE 30–1 Pharmacokinetic profiles of selected antidepressants.

Class, Drug	Bioavailability (%)	Plasma $t_{1/2}$ (hours)	Active Metabolite $t_{1/2}$ (hours)	Volume of Distribution (L/kg)	Protein Binding (%)
SSRIs					
Citalopram	80	33–38	ND	15	80
Escitalopram	80	27–32	ND	12–15	80
Fluoxetine	70	48–72	180	12–97	95
Fluvoxamine	90	14–18	14–16	25	80
Paroxetine	50	20–23	ND	28–31	94
Sertraline	45	22–27	62–104	20	98

TABLE 30–1 **Pharmacokinetic profiles of selected antidepressants.**

Class, Drug	Bioavailability (%)	Plasma $t_{1/2}$ (hours)	Active Metabolite $t_{1/2}$ (hours)	Volume of Distribution (L/kg)	Protein Binding (%)
SNRIs					
Duloxetine	50	12–15	ND	10–14	90
Venlafaxine[1]	45	8–11	9–13	4–10	27
Tricyclics					
Amitriptyline	45	31–46	20–92	5–10	90
Clomipramine	50	19–37	54–77	7–20	97
Imipramine	40	9–24	14–62	15–30	84
$5\text{-}HT_2$ antagonists					
Nefazodone	20	2–4	ND	0.5–1	99
Trazodone	95	3–6	ND	1–3	96

TABLE 30–1 Pharmacokinetic profiles of selected antidepressants.

Class, Drug	Bioavailability (%)	Plasma $t_{1/2}$ (hours)	Active Metabolite $t_{1/2}$ (hours)	Volume of Distribution (L/kg)	Protein Binding (%)
Tetracyclics and unicyclic					
Amoxapine	ND	7–12	5–30	0.9–1.2	90
Bupropion	70	11–14	15–25	20–30	84
Maprotiline	70	43–45	ND	23–27	88
Mirtazapine	50	20–40	20–40	3–7	85
MAOIs					
Phenelzine	ND	11	ND	ND	ND
Selegiline	4	8–10	9–11	8–10	99

[1]Desvenlafaxine has similar properties but is less completely metabolized.

MAOIs, monoamine oxidase inhibitors; ND, no data found; SNRIs, serotonin-norepinephrine reuptake inhibitors; SSRIs, selective serotonin reuptake inhibitors.

§ Pharmacodynamics

A. Selective Serotonin Reuptake Inhibitors

(1) Fluoxetine :

→為第一個供臨床使用之 SSRI.

(2) Paroxetine & Sertaline :

→具較短之半衰期。

(3) Adverse effects :

→headache, nausea, restlessness

§ Pharmacodynamics

A. Selective Serotonin Reuptake Inhibitors

(4) Pharmacodynamic Interaction:

→Fluoxetine or newer selective serotonin reuptake inhibitors與MAOI併用會增加monoamine 之貯存加上抑制已釋放之monoamine再吸收則會造成突觸間serotonin 濃度之顯著上升

- 此現象會導致**Serotonin Syndrome**
  - hyperthermia (高溫)
  - muscle rigidity (僵住症)
  - myoclonus (肌肉痙攣)
  - rapid change in mental status (情緒變化快速)
  - vital signs (生命特徵: Tremor、腹瀉、delirium、脈搏、呼吸、體溫...) 等之變化。

B. SNRIs

1. Tricyclics (第一代抗憂鬱劑)

【作用機轉】:

(1) 強力中樞 anticholinergic activity，而改變 adrenergic 及

serotonergic pathway.

(2) block norepinephrine 之 reuptake.

∴可以增加 NE 及 5-HT 之利用率。

使transmitters很快接近receptors.

(3) ∴長期服用

會使NE及5-HT之turnover trate↓及firing rate ↓

B. SNRIs

1. Tricyclics (第一代抗憂鬱劑)

【作用機轉】:

(4) 為中樞α_2-receptor antagonist

<I> central presynaptic α_2-adrenergic receptor 對 NE 之 release 為 negative feedback mechanism，

如 receptor agonist (clonidine)

即 decrease transmitters release;

<II> 相反如 receptor antagonist, 即增加 NE 之 release

<III> 三環抗憂鬱藥為拮抗此 receptor

∴增加 NE 之 release.

【藥理作用】

(1) CNS :

→除 protriptyline，desipramine，Nortriptyline 以外，

均有 sedation，此 sedation 對 depressant 病人有用，因

depressant 病人無法睡。

∴大部份 tricvclics 皆能減少 REM or dream sleep.

·→大量會引起 seizures

·→正常人服用 imipramine 100 mg，

無mood-elevating effect，反而有sleep，沉靜，口乾，眼花，步

伐不穩，笨拙，感到不快樂。

·但對 depressant 病人：心境開朗 (須2-3weeks)

Amoxapine (須1-2 weeks)

(但會有 DA receptor block，巴金森副作用)

【藥理作用】

(2) ANS :

→有 anticholinergic activity：amoxapine 之 anticholinergic activity最弱 (口乾、眼花、便秘、尿滯留)，

amitriptyline (Ach M block +++最強)

→有 cardiac arrhythmias

(∵ tricyclics block NE 之 reuptake 及 anticholinergic activity，增加 NE 在心臟組織的濃度，又有中樞α_2 antagonist, NE release ∴心跳快速，猝死。)

【藥理作用】

【Uses】：

(1) **Antidepressant.**

(2) **夜尿症 (Enuresis) :** 6歲以上小孩。

imipramine : 2.5 mg/kg or 50 mg/天

(∵有 anticholinergic 活性之尿滯留作用)

【副作用】：

姿態性低血壓、尿滯留、鎮靜。

2. Selective serotonin-norepinephrine reuptake inhibitors

·Venlafaxine

抑制 SERT 較強 (++)

抑制 NET 較弱 (+)、Ach M (0)、α_1 (0)

C. 5-HT_2 Antagonist

·Nefazodone (致死性肝衰竭，已少用), Trazodone 為 5-HT_{2A} 拮抗制，有 antianxiety, antipsychotic, antidepressant effect.

·相反的，如 lysergic acid (LSD) 為 5-HT_{2A} agonist.

會產生 hallucinogenic, anxiogenic

C. 5-HT_2 Antagonist

·5-HT_{2A} receptor 是 G Protein-coupled receptor.

分佈於 neocortex.

·Nefazodone 是 SERT 及 NET 弱抑制劑，但是為

postsynaptic 5-HT_{2A} 強拮抗劑。

·Trazodone 是選擇性 SERT 弱抑制劑，對 NET 作用不大。

→其代謝物 m-cpp 是強力 5-HT_{2A} 拮抗劑。

·Trazodone 常用於antidepressant.

→有弱、中度 presynapticα-adrenergic blockade 及

H_1 receptor blockade.

D. Tetracyclic and Unicyclic Antidepressants.

- **Bupropion**
  - →str. 似 ampnetamine
  - →抑制 NE，DA-reuptake in animal
  - →促進 presynaptic catecholamines release.
  - →對 5-HT 不影響。
- **Mirtazapine**
  - →為 presynaptic α_2 autoreceptor 之拮抗劑。
  - →因此促進 NE 及 5-HT 之 release.
  - →又為強力 H_1 antagonist, 所以有 sedative effect.

D. Tetracyclic and Unicyclic Antidepressants.

·**Amoxapine**

→作用與 TCAs desipramine 相似

是強力 NET inhibitor (++)

較弱 SERT inhibitor (+)

→有 postsynaptic D_2 receptor 拮抗作用

因本品為 loxapine 之代謝物 (抗精神病藥)

∴仍具有 antipsychotic 之作用

可適用於精神病人有 depression 者。

·**Maprotiline**

→作用與 TCAs desipramine 相似

E. MAO Inhibitors

【Mechanism】:

(1) 防止 catecholamine 及 5-HT 之 oxidative deamination

∴增加這些 monoamines 在腦的利用率。

→ a direct amphetamine-like stimulation.

(2) MAO Inhibitors:

·MAO-A:

→使 NE, 5-HT, tyramine 等 metabolism之amine oxidase.

→ MAO-A inh.: Moclobemide, antidepressants

·MAO-B:

→使 DA metabolism 之 amine oxidase.

→MAO-B Inh.:deprenyl, treatment of Parkinson’s disease

Table 35.4 Substrates and inhibitors for type A and type B monoamine oxidase

	Type A	Type B
Preferred substrates	Noradrenaline 5-HT	Phenylethylamine Benzylamine
Non-specific substrates	Dopamine Tyramine Deprenyl	
Specific inhibitors	Clorgyline Moclobemide	Selegiline
Non-specific inhibitors		Pargyline Tranylcypromine lproniazid

Selegiline為抗憂鬱藥，屬於monoamine oxidase inhibitors (Type B)

E. MAO Inhibitors 【藥理作用】

(1) CNS:

→提升 depressive 病人之 mood (不必 2-3 星期)。

→ sleep disorder，可以 correct.

→有中樞 stimulation 作用。

→最有效抑制 REM

(2) Cardiovascular： BP↓，理由:

→∵ NE↑，fecdback 抑制了tyrosine hydroxylase.

∴抑制 NE 之 synthesis

→又使 DA 增加，DA 於內臟血管有擴張作用。

→又興奮 hypothalamus、medulla oblongata

使NTS (Nucleus of the tractus solitarious) 興奮。

→∵BP↓

E. MAO Inhibitors

【Uses】:

(1) 使用 tricyclics 無效時，選用本品(Moclobemide)。

(2) 治療 Narcolepsy (痲醉樣昏睡)

∵抑制 REM

【相互作用】

(1) MAOI由於增加catecholamine之store，不能服含有 tyramine 食品，beer，cheese。

(2) MAO-A inh. Moclobemide不能與SSRI併用，會產生嚴重之serotonin syndrome (Tremor、腹瀉、delirium)

E. MAO Inhibitors

【註】：

MAO-B inh. Deprenyl與l-dopa, methyldopa併用易發生高血壓的危險。

小結

A. SSRIs :

Fluoxetine : SERT↓(+++)

B. SNRIs :

1. Venlafaxine : SERT (++), NET (+) (SNRIs)
2. TCAs: Amitriptyline : SERT (++), NET (+), Ach M(+++)

   (nonspecific blockers of monoamine uptake)

   ·強力Ach M 抑制 (+++) (口乾、眼花、便秘、尿滯留)

   ·又有中樞 α_2-receptor antagonist, NE release

   (cardiac arrhythmia : 因 NE 在心臟濃度↑，

   ∴心跳快速，猝死)。

C. 5-HT$_2$ Antagonist :

·Trazodone : SERT(+), NET (0), 5-HT$_2$(++)

小結

D. Tetracyclic and unicyclic :

·Bupropion : NET (0,+)

·Amoxapine : SERT (+) NET (++)

postsynaptic D_2↓ (適用於精神病人depression 者)

E. MAOIs :

·MAO-A inh. : Moclobemide.

→使NE, 5-HT 代謝之 amine oxidase↓ (antidepressant)

·MAO-B inh. : Deprenyl

→使 DA 的代謝之amine oxidase↓ (Parkinson's disease)

·Noncompetitive, nonselective, irreversible blockeros

MAO_A inh. and MOA_B inh. : phenelzine, tranylcypromine.

TABLE 30–2 Antidepressant effects on several receptors and transporters.

Antidepressant	ACh M	α_1	H_1	5-HT_2	NET	SERT
Amitriptyline	+++	+++	++	0/+	+	++
Amoxapine	+	++	+	+++	++	+
Bupropion	0	0	0	0	0/+	0
Citalopram, escitalopram	0	0	0		0	+++
Clomipramine	+	++	+	+	++	+++
Desipramine	+	+	+	0/+	+++	+
Doxepin	++	+++	+++	0/+	+	+

TABLE 30–2 Antidepressant effects on several receptors and transporters.

Antidepressant	ACh M	α_1	H_1	5-HT_2	NET	SERT
Fluoxetine	0	0	0	0/+	0	+++
Fluvoxamine	0	0	0	0	0	+++
Imipramine	++	+	+	0/+	+	++
Maprotiline	+	+	++	0/+	++	0
Mirtazapine	0	0	+++	+	+	0
Nefazodone	0	+	0	++	0/+	+
Nortriptyline	+	+	+	+	++	+

TABLE 30–2 Antidepressant effects on several receptors and transporters.

Antidepressant	ACh M	α_1	H_1	5-HT_2	NET	SERT
Paroxetine	+	0	0	0	+	+++
Protriptyline	+++	+	+	+	+++	+
Sertraline	0	0	0	0	0	+++
Trazodone	0	++	0/+	++	0	+
Trimipramine	++	++	+++	0/+	0	0
Venlafaxine	0	0	0	0	+	++

ACh M, acetylcholine muscarinic receptor; α_1, alpha$_1$-adrenoceptor; H_1, histamine$_1$ receptor; 5-HT_2, serotonin 5-HT_2 receptor; NET, norepinephrine transporter; SERT, serotonin transporter.

0/+, minimal affinity; +, mild affinity; ++, moderate affinity; +++, high affinity.

Pharacologic Differences Among Several Antidepressants

	Drug	Sedative	Antimuscarinic	Serotonin	Norepinephrine	Dopamine
1	Amitriptyline	+++	+++	+++	+	0
2	Amoxapine	++	++	+	++	+
2	Bupropion	0	0	+,0	+,0	?
1	Desipramine	+	+	0	+++	0
1	Doxepin	+++	+++	++	+	0
SSRI	Fluoxetine	+	+	+++	+,0	0,+
1	Imipramine	++	++	+++	++	0
2	Maprotiline	++	++	0	+++	0
1	Nortriptyline	++	++	+++	++	0

0:none. +:slight. ++:moderate. +++:high. ?:uncertain.

Pharmacologic Differences Among Several Antidepressants

	Drug	Sedative	Antimuscarinic	Serotonin	Norepinephrine	Dopamine
SSRI	Paroxetine	+	0	+++	0	0
1	Protriptyline	0	++	?	+++	?
SSRI	Sertraline	+	0	+++	0	0
2	Trazodone	+++	0	++	0	0

0:none. +:slight. ++:moderate. +++:high. ?:uncertain.

§ Clinical pharmacology of Antidepressants

* Clinical Indications.

A. Depression

·主要用於 major depressive disorder (MDD)

·表現在 endogenous (內生性)，vital (缺乏生命力)或自主神經等方面

·包括: 睡眠週期、食慾、性慾、活動力等之不協調。

·依病情選用藥物。

B. Anxiety Disorders

·SSRIs、SNRIs 可用於 major anxiety disorder.

包括: PTSD (post-traumatic stress disorder),OCD (obsessive-compulsive disorder), social anxiety disorder, GAD (generalized anxiety disorder),panic disorder, PMDD (premenstrual dysphoric disorder)

§ Clinical pharmacology of Antidepressants

C. Pain Disorders.

·自1960年 TCAs 即適用在因疼痛而帶來憂鬱。

·可治療 diabetic neuropathy 及 fibromyalgia.

·Fibromyalgia 纖維肌痛

→原因不明

→全身酸痛，肌肉僵硬，慢性疲勞，而帶來depression

→治療藥物 NSAID (Diclofenac) 、肌肉鬆弛劑 (solaxin)及低劑量 TCAs, SNRIs (duloxetine)，因 TCAs 作用在pain pathway上。

D. Premenstrual syndrome (PMS 經前症候群)

- 用SSRIs：Fluoxetine (Prozac)

經前症候群 (PMS)

- 1953年才開始有「經前症候群」這個名詞，經前症候群是指在月經來前兩個禮拜出現症狀，但是月經一來則會消失;而經痛是在月經間發生的
- 超過 200 症狀可能和經前症候群有關

  -頭痛、乳房脹痛、背痛、腹痛、肌肉關節酸痛、體重增加、水腫、噁心、疲勞、失眠、暈眩、性慾改變、食量增加、緊張、易怒、焦慮、沮喪、情緒改變、注意力不集中、健忘...等
- 可使用 SSRIs

山藥 Dioscoreae Rhizoma

- **古籍論述**

  -神農本草經將山藥列為上品，久服可益壽延年

  -本草綱目載:山藥治諸虛百損，療五勞七傷;除煩熱，多記事，益腎氣，健脾胃，止瀉痢，化痰涎，潤皮毛

- **成分**

  -DHEA (Dehydroepiandrosterone)

  ·固醇類荷爾蒙，為賀爾蒙的前驅物質

  ·荷爾蒙失調相關症狀，若補充 DHEA 可以改善

  ·Diosgenin, Dioscorin

- **功效**

  -改善女性的月經期或中年的更年期間，常發生的情緒不穩狀態

  -預防老化、皮膚皺紋、心臟血管疾病、記憶力衰退

  -各種老年病的相關症狀

cholesterol
Pregnenolone
孕烯醇酮
dehydroepiandrosterone(DHEA)
Progesterone
黃體酮
Androstenediol
Aldosterone
Cortisol
Androsterone
雄固酮
Testosterone
睪丸酮
5a-reductase
Estradiol(E2)
雌二醇
Dehydrotestosterone
去氫睪丸素
Estrone(E1)
雌酮
Estriol(E3)
雌三醇

E. Smoking cessation 戒菸

- ·Bupropion 自1997年用於戒菸
- ·Nicotine 也具有 antidepressant 作用，
  - ∴Bupropion 可取代其作用
- ·Nortriptyline 也可以使用

F. Obsessive-compulsive disorder

- ·可用 TCAs 之 clomipramine 治療
- ·最近使用 SSRIs (Fluoxetine) 治療之

G. Enuressis(遺尿)

·可用 Tricyclics 治療之

H. 其他：

·eating disorder （飲食失調）

·bulimia and anorexia nervosa (神經性的善饑癖與厭食症)

·cataplexy (猝發性昏倒症)

·narcolepsy (陣發性睡病)

·school phobia (厭學症)

·attention deficit disorder (意志力缺乏)

*Adverse Effects of Antidepressants

Tricyclics	
Sedation	Sleepiness,additive effects with other sedative drugs
Sympathomimetic	Tremor,insomnia
Antimuscarinic	Blurred vision(視力模糊),constipation(便秘),urinary Hesitancy(排尿遲疑),confusion
Cardiovascular	Orthostatic hypotension(姿態性低血壓),conduction defects(傳導缺陷),arrhythmias(心律不整)
Psychiatric	Aggravation of psychosis(攻擊性精神病),withdrawal Syndrome(禁戒症狀)
Neurologic	Seizeures
Metabolic-endocrine	Weight gain,sexual disturbances(性功能紊亂)

*Adverse Effects of Antidepressants

Monoamine Oxidase Inhibitors	Headache,drowsinese(思睡),drymouth,weight gain, Postural hypotension,sexual disturbance,seizure
Second-Generation Drugs Amoxapine	Similar to tricyclics;seizures dose-related
Maprotiline	Drowsiness,dizziness(暈眩),insomnia(失眠),headache, Weight loss
Trazodone,venlafaxine	Drowsiness,dizziness,insomia,headache,weight loss
Bupropion	Dizziness,dry mouth,sweating,tremor,aggravation of psychosis,potential for seizures at high dose
SSRI Fluoxetine and other serotonin reuptake inhibitors	Anxiety,insomnia,asthenia(衰弱),tremor,sweating, Gastrointestinal symptoms(胃腸症狀),rashes(發疹)

*Overdose

□ A. Tricyclics

1. overdose:dangerous

2. major effect :

(1) coma with shock, metabolic acidosis (代謝性酸中毒)

(2) respiratory depression (sudden apnea 窒息)

(3) agitation (不安) or delirium (譫妄) both before and after consciousness (知覺) is obtunded (遲鈍)

(4) neuromuscular irritability (易激) and seizure

(5) hyperpyrexia (溫度過高)

(6) bowel (腸) and bladder (膀胱) paralysis (痲痺)

(7) cardiac manifestations:conduction defects and arrhythmias.

3. 可用 Antiarrhythmic drugs, Lidocaine, Propranolol, Phenytoin, Physostigmine...治療

*Overdose

- **B. Heterocyclic Drugs**

  1. amoxapine : neurotoxicity, seizure.
  2. maprotiline : seizures, cardiotoxicity.

- **C. MAOI**

  1. Agitation (激動), delirium (譫妄), neuromuscular excitability, obtunded consciousness (反應遲鈍), seizures,shock, hyperthermia (高溫).
  2. 可用 phenothiazines 有 sedation 具有 $\alpha_1$antagonist 作用者(chlorpromazine) 治療之。

- **D. Selective Serotonin Reuptake Inhibitors**

  1. 使用 fluoxetine overdose 有死亡報告
  2. overdose : removal drugs by dialysis.

* Drug Interaction

A. Guanethidine (促進 Nereuptake) 之降血壓作用

會被tricyclics所拮抗。

B. Methyldopa (轉換成 α-methyl-NE，於medulla oblongata 是,

α_2-agonist) 之降血壓作用被 tricyclic 所拮抗。

∵tricyclics係中樞 α_2-antagonist

∴拮抗 clonidine, methyldopa.

C. Tricyclics 與 MAOI 配合

產生嚴重副作用

如:高燒 (hyperpyrexia)，convulsion，coma.

* Drug Interaction

D. Hypertension Crisis (危象)

MAOI 由於增加 catecholamines 之 store

∴與含 tyramine 之食物併用

會使交感神經↑(BP↑)

E. MAO-A Inhibitor : Moclobemide 不能與 SSRI 併用會產生嚴重之 Serotonin Syndrome (Tremor,腹瀉, delirium)。

TABLE 30–4 Antidepressant–CYP450 drug interactions.

Enzyme	Substrates	Inhibitors	Inducers
1A2	Tertiary amine TCAs, duloxetine, theophylline, phenacetin, TCAs (demethylation), clozapine, diazepam, caffeine	Fluvoxamine, fluoxetine, moclobemide, ramelteon	Tobacco, omeprazole
2C19	TCAs, citalopram (partly), warfarin, tolbutamide, phenytoin, diazepam	Fluoxetine, fluvoxamine, sertraline, imipramine, ketoconozole, omeprazole	Rifampin
2D6	Tricyclic antidepressants (TCAs), benztropine, perphenazine, clozapine, haloperidol, codeine/oxycodone, risperidone, class Ic antiarrhythmics, β blockers, trazodone, paroxetine, maprotiline, amoxapine, duloxetine, mirtazapine (partly), venlafaxine, bupropion	Fluoxetine, paroxetine, duloxetine, hydroxybupropion, methadone, cimetidine, haloperidol, quinidine, ritonavir	Phenobarbital, rifampin
3A4	Citalopram, escitalopram, TCAs , glucocorticoids, androgens/estrogens, carbamazepine, erythromycin, Ca^{2+} channel blockers, protease inhibitors, sildenafil, alprazolam, triazolam, vincristine/vinblastine, tamoxifen, zolpidem	Fluvoxamine, nefazodone, sertraline, fluoxetine, cimetidine, fluconazole, erythromycin, protease inhibitors, ketoconazole, verapamil	Barbiturates, glucocorticoids, rifampin, modafinil, carbamazepine

Mechanism of action of drugs used to treat depression	
Mechanism of actiion	**Examples**
Nonspecific blockers of monoamine uptake	Tricyclic antidepressants(amitriptyline,imipramine, Nortriptyline,clomipramine,lofepramine)
Selective serotonin reuptake inhibitors(SSRIs)	Fluoxetine,paroxetine,sertraline,citalopram
Serotonin-norepinephrine reuptake inhibitors(SNRIs)	Venlafaxine

Mechanism of action of drugs used to treat depression	
Mechanism of action	**Examples**
Noradrenergic and specific serotonergic antidepressant (NaSSA)	Mirtazapine
Selective noradrenaline reuptake inhibitor(NARI)	Reboxetine
Noncompetitive,nonselective,irreversible blockers of MAO_A and MAO_B	Monoamine oxidase inhibitors (MAOIs) (phenelzine, tranylcypromine)
Reversible inhibitors of MAO_A(RIMAs)	Moclobemide,brofaromine

St. John's Wort

- 金絲桃科植物，含金絲桃素 (hyperforin)
- 作用機轉

  -腦中神經傳遞物質，如 5-HT、NE 及 DA 的濃度↑
- 副作用

  -心悸、姿態性低血壓、口乾及便秘等
- 台灣金絲桃有:

金絲桃 (Hypericum chinese L.)

銳萼金絲桃 (Hypericum geminiflorum hemsl.) -阿里山

St. John’s Wort

藥物相互作用

- 與西藥抗憂鬱劑 (SSRI) 併服時，會導致藥物血中濃度增加造成不良反應的發生
- 臨床證實 ST. John‘s Wort 與免疫抑制劑 cyclosporin 併用時會造成 cyclosporin 的血中濃度降低，最後造成移植器官的排斥。

金絲桃

Hypericum chinense L.